

Septal Pouch in the Left Atrium

A New Anatomical Entity With Potential for Embolic Complications

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Objectives The purpose of this study was to develop a better understanding of the pathophysiology of the condition, we studied the patterns by which the septum primum (SP) and septum secundum (SS) fuse.

Background A patent foramen ovale (PFO) is a communication across the interatrial septum between a nonadherent SP and SS and is considered to be a risk factor for serious clinical syndromes.

Methods We examined the interatrial septum in 94 randomly selected autopsied hearts, with a focus on the SP and SS and the patterns by which the 2 structures fuse.

Results Of the 94 specimens that were suitable for analysis, 26 (27.66%) had a PFO. Of the remaining 68 hearts, complete fusion of the SP and SS along the entire zone of overlap was seen in 27 (28.7%) hearts. In the remaining 41 hearts (60.29%), a PFO was absent, but incomplete fusion of the SP and SS was seen. Of 41 hearts, 37 (90%) had a septal pouch that opened into the left atrial (LA) cavity. Four hearts (10%) had a pouch accessible from the right atrium. Hearts with left-sided pouches tended to be younger (50 ± 18 years of age) than hearts where there was complete fusion (age 63 ± 23 years) ($p = 0.06$).

Conclusions Our data suggest that when a foramen ovale closes spontaneously, the SP and SS fuse initially at the caudal limit of the zone of overlap of the 2 structures. This incomplete fusion results in a pouch that, in the majority of instances, communicates with the LA cavity. (J Am Coll Cardiol Intv 2010;3:98–104) © 2010 by the American College of Cardiology Foundation

A patent foramen ovale (PFO) is a communication across the interatrial septum between a nonadherent septum primum (SP) and secundum (SS). Normally present in fetal life, it closes in approximately 75% of adults. When present, it occurs equally among men and women and tends to decrease in prevalence with advancing age, from 34% during the first 3 decades of life to 20% during the ninth decade (1,2). It is considered to be a risk factor for several serious clinical syndromes, including paradoxical systemic embolism such as embolic strokes, myocardial infarction, decompression sickness in divers, and complications of pulmonary embolism (3–7). Recent evidence also suggests a link to certain types of migraines (5). The association of a PFO with these clinical problems has led to the development of techniques to achieve closure with permanently implanted devices with multiple technologies and techniques. These procedures might be associated with complications in 2% to 20% of patients, including device embolization, air embolism, device fracture, pericardial effusion, aortic laceration, residual shunt, endocarditis, and thrombus formation on the device surface (8–11). There is also a concern that a permanent implanted device might prevent future access to the left atrium (LA) for procedures such as catheter ablation of atrial fibrillation. Recent studies show that it is possible to achieve PFO closure without a permanently implanted prosthetic device. These strategies use energy application to seal the PFO closed, and success has been demonstrated in both animals and humans, although with modest efficacy (12,13). The concept of closing a PFO without leaving any foreign material behind is appealing, because it might decrease the various risks associated with an implant. As these varied techniques become increasingly popular, it becomes imperative that we develop a better understanding of the pathophysiology of the condition and, especially, “how a PFO closes when it does so spontaneously.” We carefully examined the interatrial septum in 94 randomly selected autopsied hearts, especially the SP and SS, and noted the patterns by which they fuse.

Methods

We examined 115 randomly selected postmortem adult hearts from the Jesse E. Edwards Registry of Cardiovascular Disease, John N. Nasseff Heart Hospital, St. Paul, Minnesota. Twenty-one specimens were rejected from the study due to poor condition. The specimen hearts belonged to patients with ages ranging from 17 to 90 years with a median age of 67 years. Fifty-five hearts were from men, 31 from women, and 8 were of unknown sex. Disease processes associated with these specimens included atherosclerotic coronary artery disease (atherosclerotic arteries with a normal sized ventricle and no infarction), atherosclerotic coronary heart disease (atherosclerotic coronary arteries with evidence of myocardial infarction), cardiac and/or ventricular hypertrophy, dilated cardiomyopathy, cardiac enlargement (including atrial enlargement), rheumatic heart disease, infective endocarditis, valvular heart disease, and other diagnoses as labeled by the Cardiovascular Registry (Table 1).

Each specimen was carefully inspected to identify the structures unique to the right atrium (RA), starting with the inferior vena cava (IVC), the superior vena cava, the coronary sinus, and the tricuspid annulus. These landmarks were used to identify the cranial, caudal, anterior, and posterior aspects of the heart as well as to distinguish the RA from the LA. The LA was identified on the basis of the mitral valve and pulmonary veins. For the purposes of describing and measuring the dimensions of the fossa ovalis, we assigned a cranial spatial vector in the direction of the superior vena cava and a caudal vector in the direction of the IVC. The anterior location was assigned to the vector in the direction of the septal leaflet of the tricuspid valve and the posterior vector in the opposite

Abbreviations and Acronyms

IVC	= inferior vena cava
LA	= left atrium/atrial
LSP	= left-sided pouch
PFO	= patent foramen ovale
RA	= right atrium/atrial
RSP	= right-sided pouch
SP	= septum primum
SS	= septum secundum
TEE	= transesophageal echocardiogram

Table 1. Demographic Data of Hearts Examined

	Age, yrs (Mean ± SD)	Sex	Major Disease Processes				
			Noncardiac Death	CAD	Idiopathic CMP	Valvular Disease	Misc.
Hearts (n = 94)	50 ± 21	55 M; 31 F; 8 UNK	19	19	11	14	31
PFO (n = 26)	58 ± 18	14 M; 9 F; 3 UNK	6	2	4	4	10
PFO absent—complete fusion (n = 27)	63 ± 23	16 M; 11 F	3	8	4	4	8
PFO absent—left-sided pouch (n = 37)	50 ± 18	26 M; 9 F; 2 UNK	9	7	3	6	12
PFO absent—right-sided pouch (n = 4)	30 ± 17	2 M; 1 F; 1 UNK	1	2	0	0	1

Demographic data of hearts examined, including underlying disease processes. The miscellaneous (Misc.) category includes Wolf-Parkinsons-White syndrome, endocarditis, hypertrophic cardiomyopathy, aortic dissection, and hearts from patients with malignancies.

CAD = coronary artery disease; CMP = cardiomyopathy; F = female; M = male; PFO = patent foramen ovale; UNK = unknown.

direction. When the fossa ovalis demonstrated outpouching of more than 11 mm beyond the atrial septum, an atrial septal aneurysm was considered to be present (14).

The junction of the fossa ovalis with the limbus was probed with a 1-mm-diameter probing rod. If this structure could be passed into the LA, that heart was defined as having a PFO (Fig. 1D). If a part of the fossa ovalis was absent, the heart was defined as having an ostium secundum atrial septal defect. We classified the specimens in terms of the presence or absence of a PFO or atrial septal defect. When a PFO was absent, the interatrial septum was further examined to assess for completeness of fusion of its components. With the same cylindrical probing rod, we probed the zone of overlap between the SP and the SS from both the RA and LA (Figs. 2A, 2B, and 2C). When incomplete fusion was present, we further characterized the specimens

on the basis of the location of the fusion and whether a pouch was present that could be accessed from the RA (right-sided pouch [RSP]: Figs. 1C or 2C) or LA (left-sided pouch [LSP]: Figs. 1B, 2A, and 2B). The depths of these pouches were measured by introducing a probing rod (Figs. 2A and 2B), and this maneuver was performed in all the hearts with pouches. In 54 of the 94 hearts (11 of 26 hearts with PFOs; 43 of 68 hearts where PFO was absent [23 of 27 hearts with complete fusion of SP and SS; 19 of 37 hearts with LSP; 1 of 4 hearts with RSP]), measurements of the fossa ovalis were made in the cranial-to-caudal direction (vector A) and the anterior-to-posterior direction (vector B). In these hearts, the area of the fossa ovalis was estimated on the basis of the assumption that it has an oval shape ($\text{area} = \pi AB/4$). We also examined all 94 heart specimens for the presence of a Eustachian valve (valve at

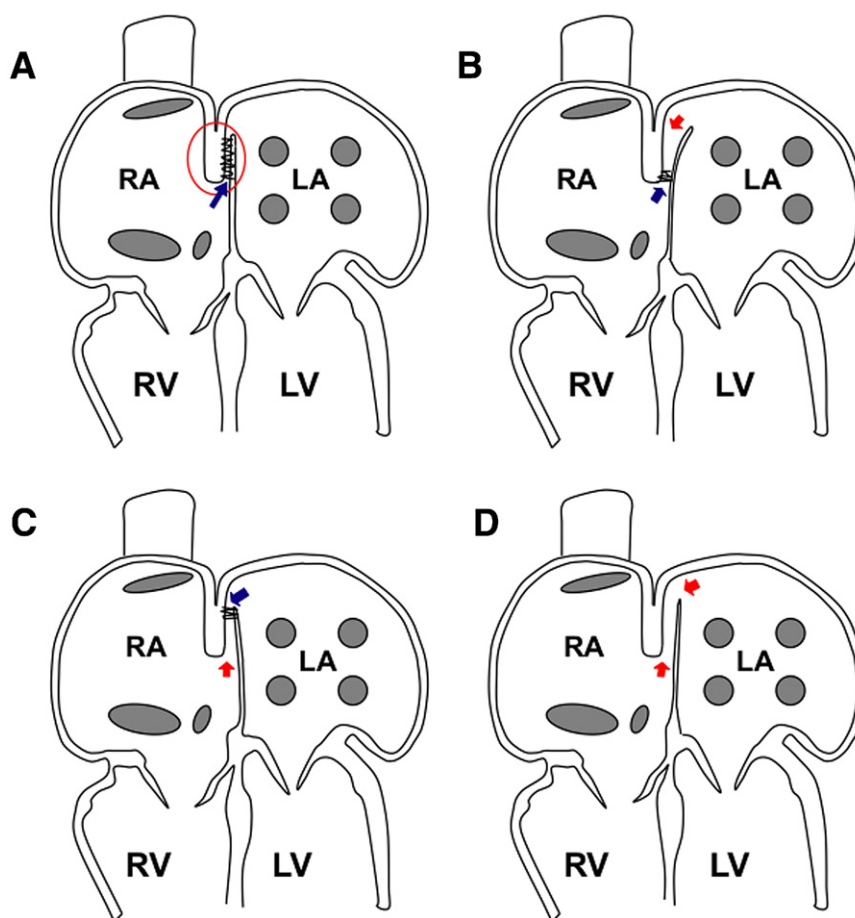


Figure 1. Patterns of Fusion in the Atrial Septum

Cartoon illustrating the variations in fusion along the zone of overlap of the septum primum and secundum. (A) Fusion between the septum primum and secundum occurs along the entire zone of overlap. (B) Fusion between the septum primum and secundum is limited to the caudal portion of the zone of overlap (blue arrow) resulting in a pouch that can be accessed from the left atrium (LA) (red arrow). (C) Fusion is limited to the cranial portion of the zone of overlap (blue arrow); the resulting pouch can be accessed from the right atrium (RA) (red arrow). (D) Lack of fusion between the septum primum and secundum with a resulting patent foramen ovale (red arrows). LV = left ventricle; RV = right ventricle.

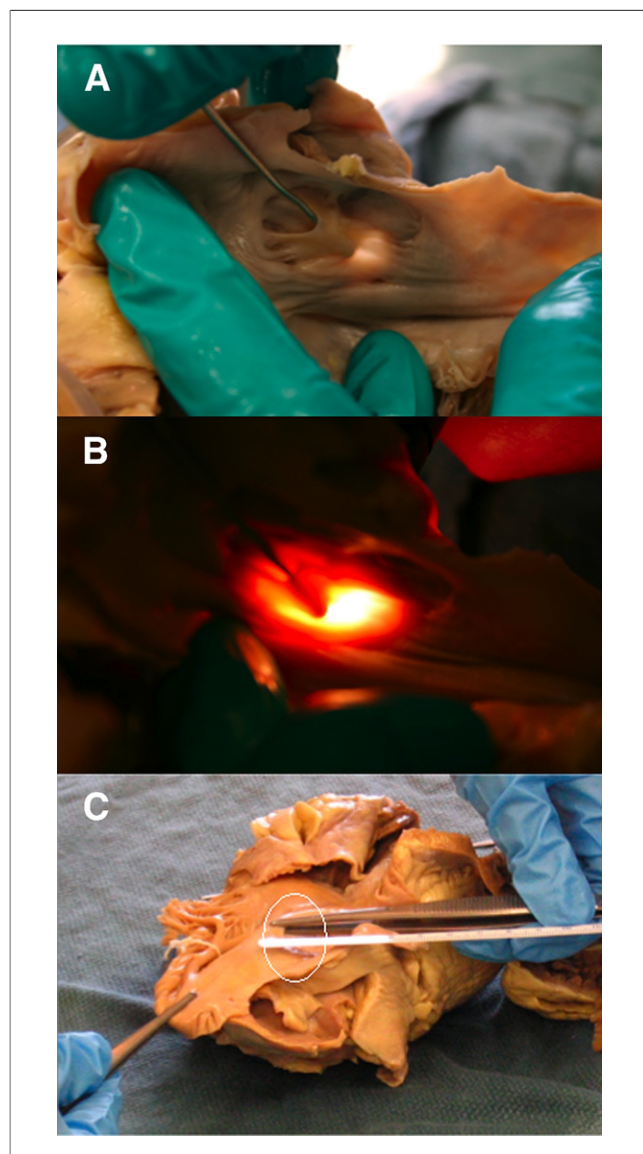


Figure 2. Illustration of Atrial Septal Diverticula

Autopsy specimen demonstrating a pouch accessible from the left atrium. A probing rod, accessed from the left atrium, is placed within this pouch. **(A)** Ambient light is seen to selectively transilluminate the fossa ovalis, providing a better appreciation of the zone of overlap between the septum primum and secundum. **(B)** Flashlight placed in the right atrium selectively transilluminates the fossa ovalis. **A and B** illustrate fusion limited to the caudal portion of the zone of overlap, resulting in a pouch accessible from the left atrium. **(C)** Right-sided pouch. Postmortem heart specimen showing the presence of a right-sided pouch (white ellipse). The limbs of the forceps are seen to grasp the septum secundum, with 1 limb of the forceps inside the pouch.

the distal end of the IVC at the junction with the RA) and a Thebesian valve (valve at the ostium of the coronary sinus).

Categorical variables were summarized as percentages. Continuous variables were expressed as mean \pm SD and compared with 2-tailed Student *t* tests.

Results

The demographic data of the hearts examined, including the underlying disease processes, are shown in Table 1. There were 6 specimens with congenital heart disease (5 with unicuspid aortic valve, and 1 with bicuspid aortic valve). The collection of data and sequence of data analysis are illustrated in the flow diagram shown in Figure 3. The focus of this study was on hearts where the SP and SS had fused completely or partially, and therefore a PFO was absent. Of the 94 specimens that were suitable for analysis, 26 (27.7%) had a PFO.

Of the remaining 68 hearts, complete fusion of the SP and SS along the entire zone of overlap (similar to Fig. 1A) was seen in 27 (39.7%) hearts. In the remaining 41 hearts (60.3%), a PFO was absent, but incomplete fusion of the SP and SS was seen (Figs. 2, 4, and 5). Of 41 hearts, 37 (90%) had a pouch with its opening located on the left side of the interatrial septum (LSP) (Figs. 2 and 4, similar to Fig. 1B). Four hearts (9.8%) had a pouch accessible from the RA (RSP) (Fig. 2C, similar to Fig. 1C). The LSPs had a depth of 8.3 mm (SD \pm 3.47 mm), and the RSPs had a depth of 5.38 mm (SD \pm 2.06 mm).

The cranio-caudal and transverse dimensions of the fossa ovalis in all hearts where these measurements were made (54 of 94 hearts) were 18.3 ± 4.5 mm and 17 ± 4.5 mm, respectively. The area of the fossa was 264 ± 132.0 mm². In hearts where a PFO was present, the transverse dimension was 17 ± 3.4 mm and the cranio-caudal dimension was 17.1 ± 4.7 mm, with an area of 240.2 ± 116 mm². Among hearts without a PFO (*n* = 68), a transverse dimension of 17 ± 4.4 mm and a cranio-caudal dimension of 17.9 ± 4.06 mm with an area of 247.5 ± 120 mm² was seen. There was no statistical significance upon comparing the fossa dimensions between the 2 groups (i.e., hearts with a PFO vs. those without a PFO). In hearts with LSPs (*n* = 37), the cranio-caudal and transverse dimensions were 16.5 ± 3.32 mm and 16 ± 3.27 mm with an area of 206.29 ± 82.18 mm². In hearts where there was complete fusion between the SP and SS, measurements of the fossa ovalis were made in 23 of 27 specimens. The mean cranio-caudal and transverse dimensions were 19.22 ± 4.30 mm and 18.09 ± 4.93 mm, respectively, and the area was 285.7 ± 136.3 mm². There was a statistically significant difference (*p* < 0.017) between the fossa dimensions of the groups where an LSP was present versus hearts with completely fused septal components. Hearts with LSP tended to be younger (50 ± 18 years of age) than hearts where there was complete fusion (63 ± 23 years of age) (*p* = 0.06). Fourteen of the hearts had features consistent with an atrial septal aneurysm. A PFO was present in 11 of these hearts, a LSP was seen in 2, and complete fusion was seen in 1.

We also examined all hearts for the presence of a Eustachian and a Thebesian valve. Of the hearts with a

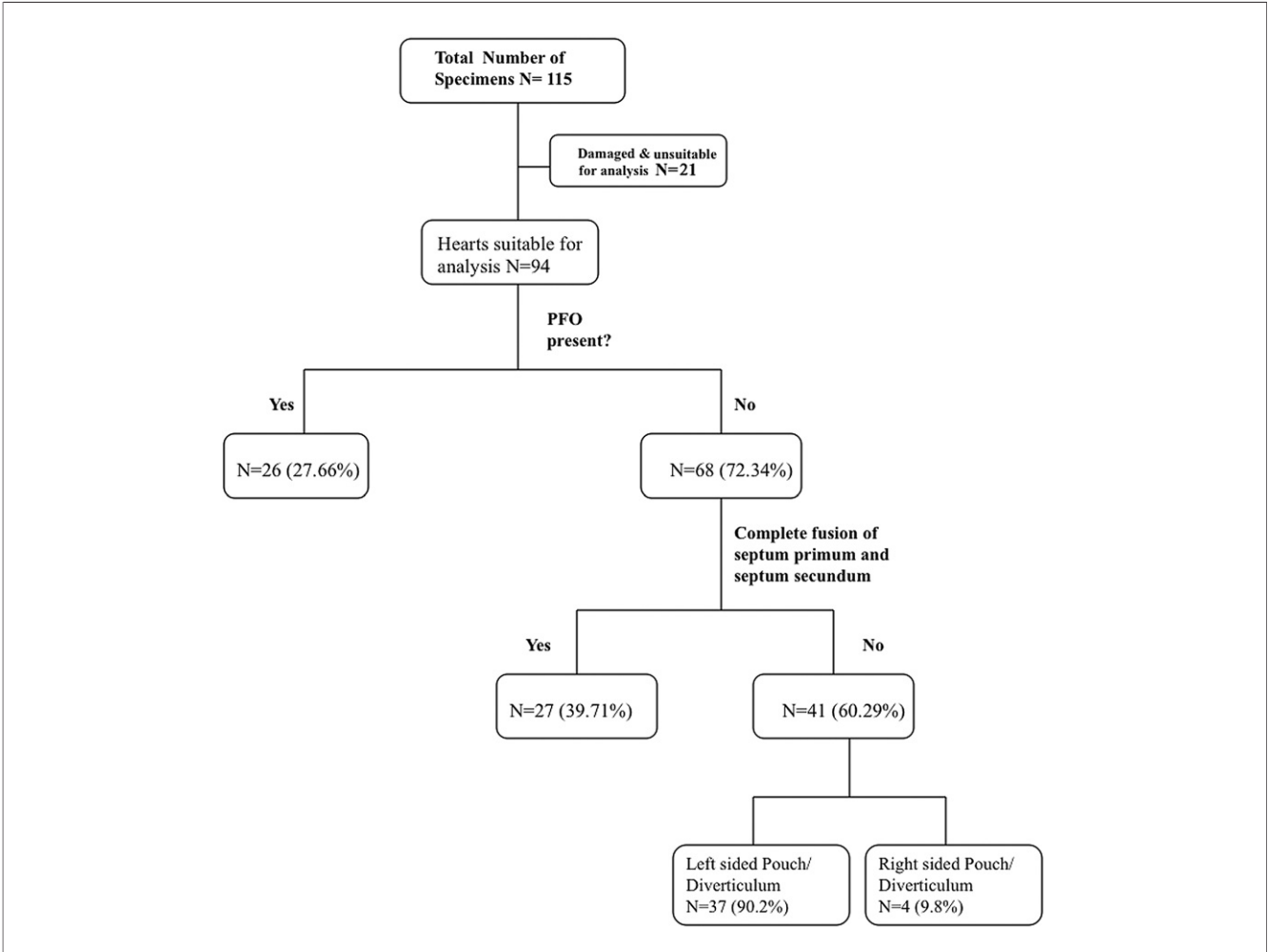


Figure 3. Schema Indicating Data Collection and Analysis

Flow diagram illustrating the collection of data and sequence of data analysis. The focus of this study was on hearts where patent foramen ovale (PFO) was excluded (68 of 94 hearts examined).

PFO, 22 of 26 hearts had a Eustachian valve (5.24 ± 4.1 mm in dimension), and a Thebesian valve was present in 20 of the hearts in this group. In specimens where a complete fusion was present between the SP and SS, a Eustachian valve was seen in 26 of 27 hearts with dimensions of 5.34 ± 2.6 mm. A Thebesian valve was seen in 23 of 27 hearts in this group. In the group with LSP, a Eustachian valve was seen in 32 of 37 hearts and was measured at 4.53 ± 2.7 mm. In this group, a Thebesian valve was seen in 29 of 37 hearts. A Eustachian valve (4.9 ± 2.3 mm) and a Thebesian valve were seen in all 4 hearts with an RSP.

Discussion

Natural history of PFO closure. The interatrial septum is composed of the SP and SS. The SS overlaps the opening of the SP and functions as a door frame, with the SP functioning as a door (7). In utero, the RA pressure is

higher than the LA, with the pressure gradient keeping the SP separated from the SS. The foramen ovale thus stays open during fetal life, providing the necessary conduit for RA to LA shunting of oxygenated blood to the systemic circulation bypassing the lungs. With the first breath, the resistance in the pulmonary vascular bed decreases, causing a simultaneous decrease in RA pressure and an increase in LA pressure. This forces the SP against the SS, achieving physiological closure. Over time, the development of adhesions serves to close the foramen in up to 75% of adults. In 25%, adhesions fail to form, resulting in a PFO (1,2,7). Our observations strongly suggest that in the majority of instances, when fusion does occur between the SP and SS, it does not occur along the entire zone of overlap. In our study of the interatrial septum, a PFO was seen in 27% of hearts analyzed (26 of 94), similar to findings in prior published studies. In the remaining hearts, the majority of the time,

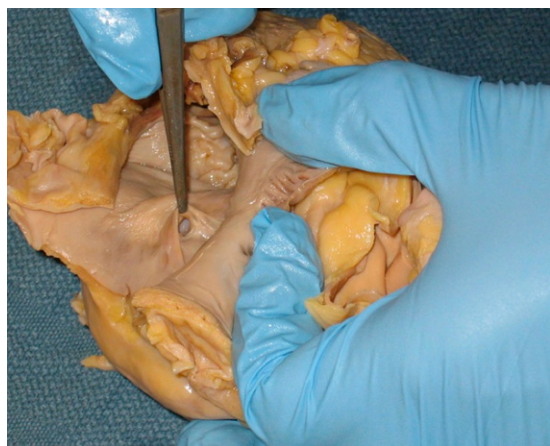


Figure 4. Intracavitary View of an LSP

Intracavitary view of the left-sided pouch (LSP) in a heart with fusion of the septum primum and secundum limited to the caudal portion of the zone of overlap. One of the jaws of the forceps is inserted into the LSP. The cranial limit of the septum primum is then grasped with the forceps and pulled apart from the septum secundum, providing an intracavitary view of the pouch.

the septal components did not fuse completely along the zone of overlap (41 of 68 hearts) and thus gave rise to pockets. When fusion occurs at the caudal limit of the zone of overlap, a pouch is seen to result that opens into the LA. In hearts with incomplete fusion of the septal components, this is what is seen most of the time (37 of 41 hearts). An RSP due to fusion at the cranial limit of the zone of overlap was an uncommon finding (4 of 41).

These observations lead us to believe that when the SP and SS come together at the time of birth, the constant motion and friction-induced injury cause adhesions to form initially at the caudal portion of the zone of overlap. In some, the adhesions then possibly progress in a cranial direction. From our data, it is not clear as to whether a PFO, an LSP, and a completely fused septum represent a continuum. According to this hypothesis, the natural history of PFO closure consists of fusion between the SP and SS occurring at first at the caudal limit of the zone of overlap and over time progressing to involve the entire zone of overlap. The fact that hearts with incomplete fusion of the SP and SS tend to belong to younger individuals supports this contention (i.e., as one ages, initially the PFO closes with an LSP as the first stage). This is followed later by complete fusion along the zone of overlap. Our data also suggest that closure of PFOs is an ongoing process that might occur throughout the lifetime of an individual. It might also explain why the prevalence of PFOs decreases with advancing age (1). The PFO size increases with each decade of life, perhaps reflecting size-based selection over time, where larger PFOs remain patent while smaller ones close.

Clinical significance. We have also observed this pouch in live patients with transesophageal echocardiograms (TEEs), intra-cardiac echocardiograms, and multislice computed tomography angiograms. In a separate follow-up project, we are examining the prevalence of incomplete fusion of the SP and SS as detected by TEE. To emphasize the clinical relevance of our findings, we include an example of an LSP as demonstrated with still TEE images (Fig. 5).

To our knowledge, our observations of atrial septal anatomy are entirely novel. Proper identification of the fossa ovalis is crucial for procedures such as a transseptal puncture and achieving artificial closure of PFOs. An improved understanding of the fossa ovalis and its components will, we believe, lead to a better understanding of its role in conditions such as cryptogenic strokes and improve procedures such as closure of PFOs. Until recently, percutaneous closures of PFO required the implantation of permanent devices. Recent investigations have explored energy application to achieve PFO closure without leaving any device behind and have demonstrated

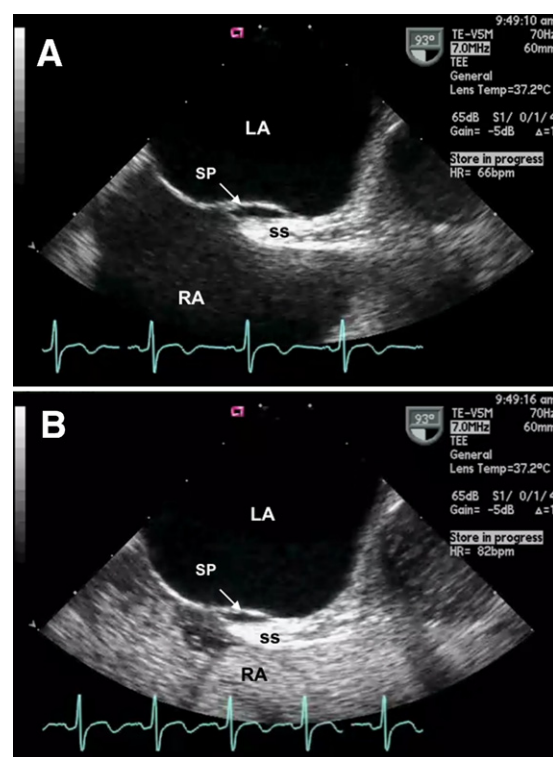


Figure 5. Demonstration of Atrial Septal Pouch With TEE

(A) Transesophageal echocardiogram (TEE) illustrating incomplete fusion along the zone of overlap between the septum primum (SP) and septum secundum (SS). (B) Interatrial communication was excluded with agitated contrast injection with a Valsalva maneuver demonstrating no bubbles crossing the interatrial septum. Of note: no bubbles are seen within the pouch, confirming that this is an LSP. With atrial contraction, the distance between SP and SS along the zone of overlap varies significantly (A and B). Abbreviations as in Figures 1 and 4.

success in both animals and in humans, although with modest efficacy (12,13). The underlying principle seems to be the generation of an inflammatory response from the thermal injury with formation of a platelet/fibrin thrombus and subsequent scar. We believe our data support this concept and suggest that this mechanism might represent and replicate the natural history of PFO closure. Therefore, techniques developed to artificially achieve closure of a PFO do not need to generate fusion along the entire zone of overlap. The presence of an LA pouch with access to the systemic circulation also raises the possibility that, similar to the LA appendage, during low-flow states, this pouch might serve as a site for thrombus formation and embolization. In addition to serving as a conduit for emboli, it has also been suggested that a thrombus might form within the tunnel of a PFO due to stagnant blood (15). Although this is pure conjecture, we believe it will be much more likely for blood to stagnate in a blind pouch and thus form a thrombus rather than within a tunnel such as a PFO. A review of published data reveals clinical descriptions of thrombi in an LSP related to incomplete fusion of the interatrial septum, with remarkable similarity to our description (16,17). We have also come across reports of thrombi in the LA cavity attached to the interatrial septum (suggesting that the site of origin and attachment might be the LSP) (18). It is noteworthy that, in the setting of rheumatic heart disease, the LA appendage is the site of thrombus formation in only 50% of patients (19). Especially in these patients, an LSP might be an important thrombogenic site. We hope that our findings will stimulate systematic investigations of this structure, especially in patients with cryptogenic stroke.

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Key Words: adhesions ■ autopsy ■ closure ■ patent foramen ovale ■ stroke.